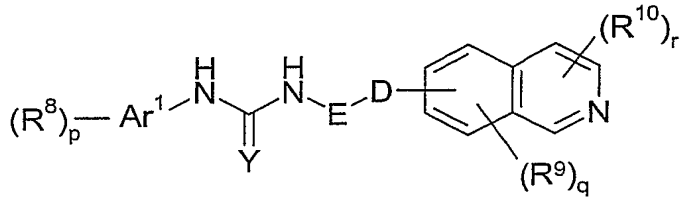
Claims

1. Isoquinoline derivatives of formula I



I

wherein

Ar^1 is selected from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

E is $(CR^5R^6)_n$, wherein n is 1 or 2,

D is $(CR^5R^6)_k$, wherein k is 0 or 1,

R^5, R^6 are in each case independently from one another selected from H and A;

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,

$(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nCH$=N-R^{11}, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S,

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, preferably from the group consisting

of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy and alkoxyalkyl,

Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one ore more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein

Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3,

k, n and m are independently of one another 0, 1, 2, 3, 4, or 5,

Y is selected from O, S, NR^{21}, $C(R^{22})$-NO_2, $C(R^{22})$-CN and $C(CN)_2$, wherein

R^{21} is independently selected from the meanings given for R^{13}, R^{14} and

R^{22} is independently selected from the meanings given for R^{11}, R^{12},

p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

and

Hal is independently selected from a group consisting of F, Cl, Br and I;

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

2. Isoquinoline derivatives according to claim 1,

wherein

Ar^1 is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

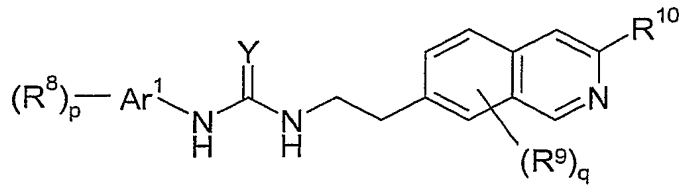
R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, and/or are independently selected from a group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,

p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

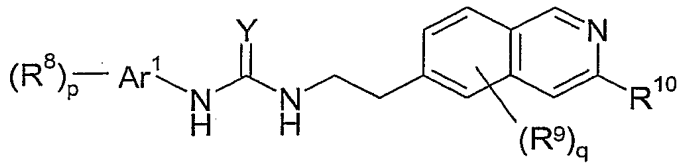
r is 0, 1, 2, or 3, preferably 0, 1 or 2;

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof

3. Isoquinoline derivative according to claim 1 or 2, selected from the compounds of formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, IL, Im, In, Io, Ip, Iq and Ir,



Ia



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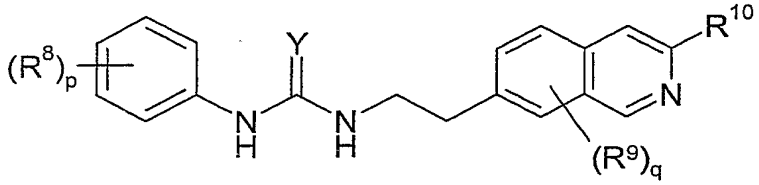
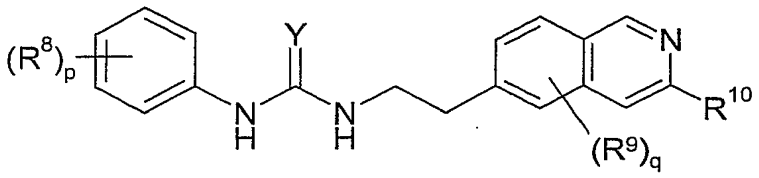
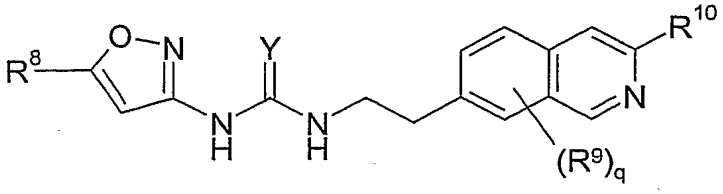


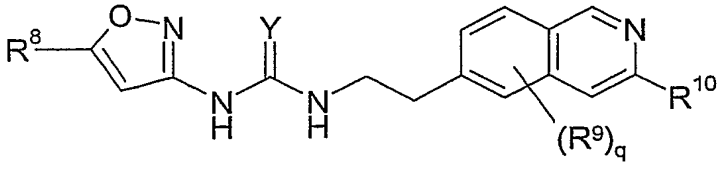
Ic



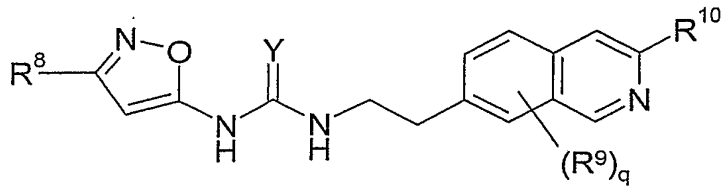
Id



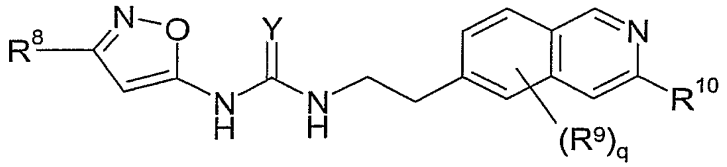
Ie



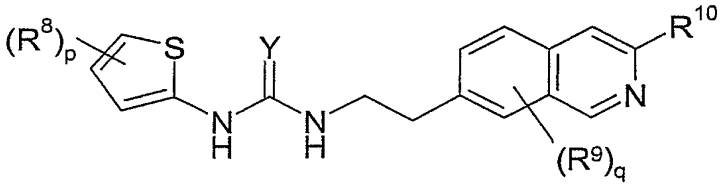
If



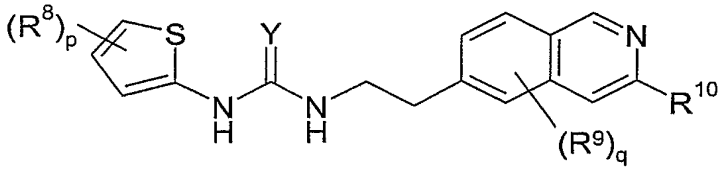
Ig



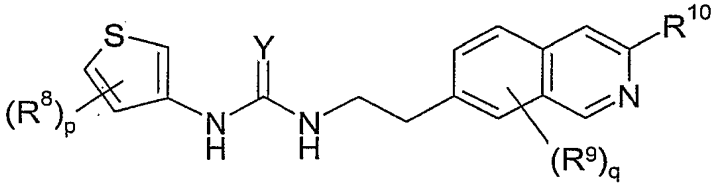
Ih



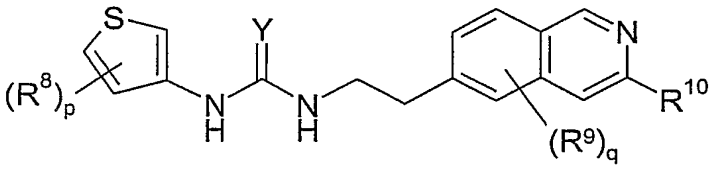
Ii



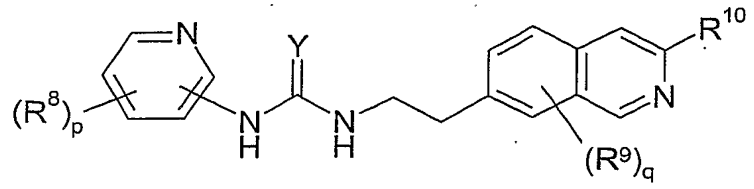
Ij



Ik



IL



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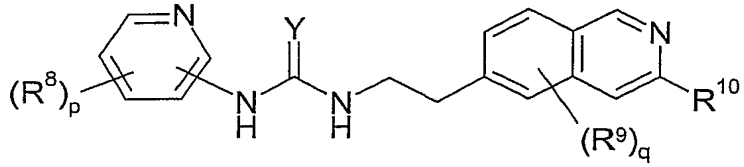
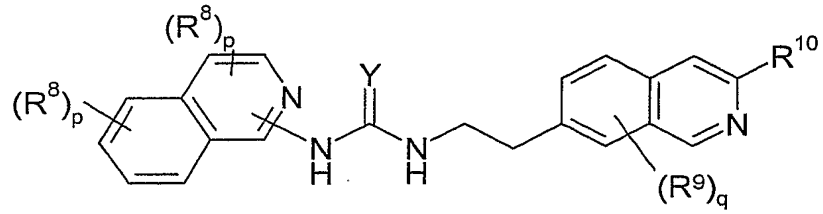
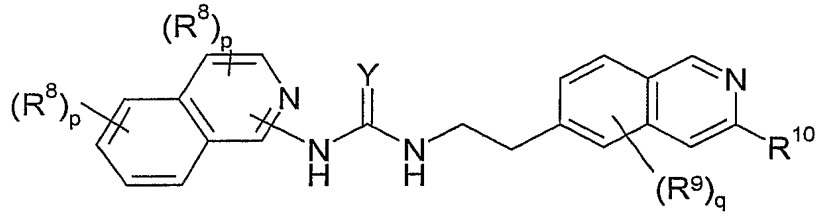


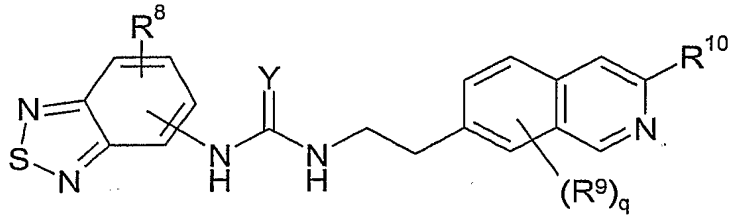
In



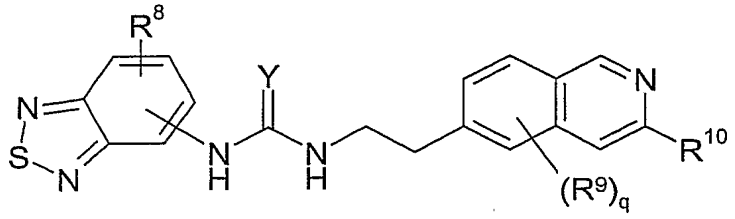
Io



Ip



Iq



Ir

wherein R^8, R^9, R^{10}, Y, p and q are as defined in claim 1 or2, R^{10} is H or as defined in claim 1 or 2; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

4. Isoquinoline derivative according to claim one of the claims 1 to 3, selected from
7-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-(2-{3-[Chloro-(2-dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-ethyl)-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Chloro-2-methoxy-5-methyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(Fluoro-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-(2-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-ethyl)-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Methyl-3-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(3-Trifluoromethanesulfonyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(3-Trifluoromethoxy-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Fluoro-3-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(3-Trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(5-Chloro-2-methoxy-4-methyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;

7-{2-[3-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
and the pharmaceutically acceptable derivatives, salts and solvates thereof.

5. Isoquinoline derivative according to one of the claims 1 to 4 as a medicament.

6. Isoquinoline derivative according to one of the claims 1 to 4 as a kinase inhibitor.

7. Isoquinoline derivative according to claim 6, characterized in that the kinases are selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.

8. Pharmaceutical composition, characterised in that it contains one or more compounds according to one of the claims 1 to 4.

9. Pharmaceutical composition according to claim 8, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 4.

10. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 4 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 4, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or

administration to a patient.

11. Use of a compound according to one of the claims 1 to 4 as a pharmaceutical.

12. Use of a compound according to one of the claims 1 to 4 in the treatment and/or prophylaxis of disorders.

13. Use of a compound according to one of the claims 1 to 4 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.

14. Use according to claim 12 or 13, characterised in that the disorders are caused, mediated and/or propagated by one or more kinases, selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.

15. Use according to claim 12, 13 or 14, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.

16. Use according to claim 12, 13, 14 or 15, characterised in that the disorder is cancer.

17. Use according to claim 12, 13, 14 or 15, characterised in that the disorder is noncancerous.

18. Use according to claim 12, 13, 14, 15 or 17, characterised in that the disorders are selected from the group consisting of psioarsis, arthritis, inflammation, endometriosis, scarring, Helicobacter pylori infection, Influenza A, begnin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

19. Use according to one of the claims 12 to 16, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, ovarian cancar, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.

20. Use according to one of the claims 12 to 17, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors, rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.

21. Use according to one of the claims 12 to 15, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.

22. Use of a compound according to one of the claims 1 to 4 as a kinase inhibitor.

23. Use according to claim 22, characterised in that the kinase is one or more kinases kinases selected from the group consisting of from raf-kinases, Tie-kinases, PDGFR-kinases, VEGFR-kinases and p38-kinases.

24. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 4 is administered to a patient in need of such a treatment.

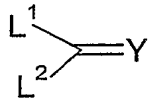
25. Method according to claim 24, characterised in that the one or more compounds according to one of the claims claim 1 to 4 are administered as a pharmaceutical composition according to claim 8 or 9.

26. Method for the treatment and/or prophylaxis of disorders according to claim 25, characterised in that the disorders are as defined in one of the claims 14 to 21.

27. Method for the treatment according to claim 26, characterised in that the disorder is cancerous cell growth mediated by by raf-kinase, Tie kinases, PDGFR kinases and/or VEGFR kinases.

28. Method for producing compounds of formula I, characterised in that

a) a compound of formula II,



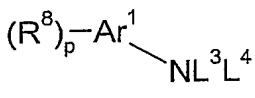
II

wherein

L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

is reacted with

b) a compound of formula III



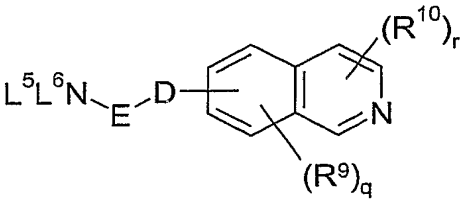
III

wherein

L^3 and L^4 are independently from one another H or a metal ion, and wherein R^8, p and Ar^1 are as defined in claim 1,

and

c) a compound of formula IV,



IV

wherein

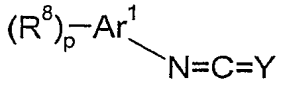
L^5 and L^6 are independently from one another H or a metal ion, and E, D, R^9, q, R^{10} and r are as defined in claim 1,

and optionally

d) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

29. Method for producing compounds of formula I, characterised in that

a) a compound of formula IIIb



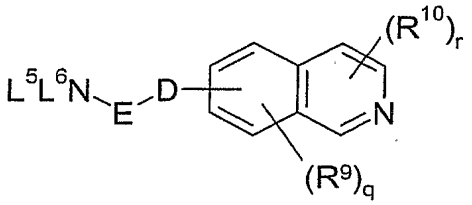
IIIb

wherein

wherein R^8, Ar^1, p and Y are as defined above and below,

and

b) a compound of formula IV,



IV

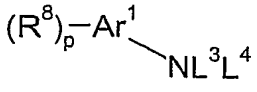
wherein

L^5 and L^6 are independently from one another H or a metal ion, and E, D, R^9, q, R^{10} and r are as defined above and below,

and optionally

c) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

30. Compound of formula III,



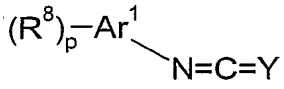
III

wherein

L^3 and L^4 are independently from one another H or a metal ion, and wherein R^8, p and Ar^1 are as defined in claim 1.

31. Compound of formula IIIb,

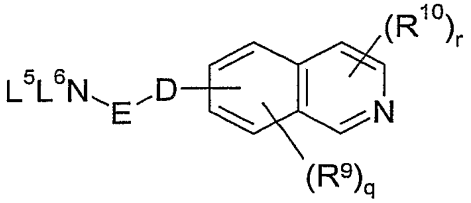
wherein



IIIb,

R^8, p, Ar^1 and Y are as defined in claim 1.

32. Compound of formula IV,



IV

wherein

L^5 and L^6 are independently from one another H or a metal ion, and E, D, R^9, q, R^{10} and r are as defined in claim 1.